a. Bacterial reverse mutation assays

As shown in Table 18, glyphosate was not mutagenic in any of the *in vitro* bacterial mutation assays using *S. typhimurium* or *E. coli* tester strains with or without microsomal S9 metabolic activation. These results are consistent with the negative findings in the previously reviewed EPA guideline (870.5100) bacterial reverse gene mutation study (MRID 00078620).

Table 18. Results from Bacterial Reverse Gene Mutation Assays[1]

Author	Cell/Strain[2]	Purity	Highest test concentration	Results –S9	Results +S9
Akanuma, M. (1995)	TA98, TA100, TA1535, TA1537; WP2*uvr*A	95.7%[3]	5000 µg/plate	Negative	Negative
Callander, R.D. (1996)	TA98, TA100, TA1535, TA1537; WP2P and WP2*uvr*A	95.6%[3]	5000 µg/plate	Negative	Negative
Flügge, C.(2010)	TA98, TA100, TA102, TA1535, TA1537	76.1%[4]	100 µg/plate	Negative	Negative
Flügge, C. (2010)	TA98, TA100, TA102, TA1535, TA1537	96.4%	3160 µg/plate	Negative	Negative
Flügge, C.(2009)	TA98, TA100, TA102, TA1535, TA1537	98.8%	3160 µg/plate	Negative	Negative
Jensen, J.C. (1991)	TA98, TA100, TA1535, TA1537	98.6%	2500 µg /plate w/o S9; 5000 µg /plate w/ S9	Negative	Negative
Li and Long (1998)	TA98, TA100, TA1535, TA1537, TA1538;	98%	5000 µg/plate	Negative	Negative
NTP (1992)	TA97, TA100, TA1535	98%	10,000 µg /plate	Negative	Negative
Schreib, G. (2010)	TA98, TA100, TA1535, TA1537; WP2*uvr*A	96%	5000 µg/plate	Negative	Negative
Shirasu et al. (1978)	TA98, TA100, TA1535, TA1537, TA1538 and WP2*uvr*A	98.4%	5000 µg/plate	Negative	Negative
Sokolowski, A. (2007c)	TA98, TA100, TA1535, TA1537; WP2*uvr*A	95.0%	5000 µg/plate	Negative	Negative
Sokolowski, A. (2007a)	TA98, TA100, TA1535, TA1537; WP2uvrA	95.1%	5000 µg/plate	Negative	Negative
Sokolowski, A. (2009b)	TA98, TA100, TA1535, TA1537;WP2P and WP2*uvr*A	96.3%	5000 µg/plate	Negative	Negative
Sokolowski, A. (2009a)	TA98, TA100, TA1535, TA1537; WP2*uvr*A	96.66%	5000 µg/plate	Negative	Negative
Sokolowski, A. (2007b)	TA98, TA100, TA1535, TA1537; WP2*uvr*A	97.7%	5000 µg/plate	Negative	Negative
Suresh, T.P. (1993)	TA98, TA100, TA1535, TA1537, TA1538	96.0%	1000 µg/plate	Negative	Negative
Thompson, P.W. (1996)	TA98, TA100, TA1535, TA1537; WP2*uvr*A	95.3%	5000 µg/plate	Negative	Negative

1. Studies cited in Williams *et al.*, (2000), Kier and Kirkland (2013), or IARC monograph.
2. *Salmonella typhimurium* strains (TA97, TA98, TA100, TA102, TA1535, TA1537, and/or TA1538) or *E. coli* strains (WP2P and WP2*uvr*A)
3. Glyphosate acid
4. Monoammonium glyphosate salt

b. *In vitro* mammalian cell gene mutation assays

Glyphosate did not induce forward mutations in mouse lymphomas cells or Chinese hamster ovary (CHO) cells in the presence or absence of metabolic (S9) activation (Table 19).

Table 19. Results from mammalian gene mutation assays[1].

Author	Assay Type	Cell type	Purity	Highest conc.	Result -S9	Result +S9
Clay (1996)	*In vitro* mammalian gene mutation	L5178Y mouse lymphoma cells/ tk locus	95.6%	1.0 mg/mL	Negative	Negative
Jensen, J.C. (1991)	*In vitro* mammalian gene mutation	L5178Y mouse lymphoma cells/ tk locus	98.6%	5.0 mg/mL	Negative	Negative
Li and Long (1988)	*In vitro* mammalian gene mutation	CHO cells/ HGPRT locus	98%	22.5 mg/mL	Negative	Negative

1. Studies cited in Williams *et al.*, (2000), Kier and Kirkland (2013), or IARC monograph.

c. *In vitro* chromosomal aberration assays

Lioi *et al.*, reported positive findings for chromosomal aberrations in human and bovine lymphocytes treated with glyphosate *in vitro* in the absence of S9 activity. However, Van de Waart reported no significant increase in chromosomal aberrations in human lymphocyte treated with up to 0.56 mg/mL (-S9) and 0.33 mg/mL (+S9) glyphosate, a concentration more than 3 orders of magnitude higher than where Lioi *et al.* reported aberrations. Glyphosate was negative in two other *in vitro* chromosomal aberrations studies in human lymphocytes (Fox, 1998 and Manas, 2009) and did not induce chromosomal aberrations in Chinese hamster lung cells (Matsumoto, 1995 and Wright 1996). A summary of the findings is presented in Table 20.

Table 20. Results from *in vitro* chromosomal aberration assays[1].

Authors	Assay	Cell type	Purity	Highest test concentration	Result -S9	Result +S9
Van de Waart (1995)	Chromosomal Aberration	Human peripheral lymphocytes	>98%	0.56 mg/mL with S9; 0.33 mg/mL w/o S9	Negative	Negative
Fox, V. (1998)	Chromosome Aberration	Human peripheral lymphocytes	95.6%[2]	1250 ug/mL	Negative	Negative
Lioi et al. (1998a)	Chromosomal Aberration	Human peripheral lymphocytes	>98%	1.4 µg/mL	Positive	Not Tested
Manas et al. (2009)	Chromosomal Aberration	Human peripheral lymphocytes	96%	6 mM	Negative	Not Tested
Lioi et al. (1998b)	Chromosomal Aberration	Bovine peripheral lymphocytes	>98%	2.9 mg/L	Positive	Not Tested

Matsumoto, K. (1995)	Chromosomal Aberration	Chinese Hamster Lung (CHL) cells	95.68%[2]	1000 ug/mL	Negative	Negative
Wright, N.P. (1996)	Chromosomal Aberration	Chinese Hamster Lung (CHL) cells	95.3%	1250 ug/mL	Negative	Negative

1. Studies cited in Williams *et al.*, (2000), Kier and Kirkland (2013), or IARC monograph.
2. Glyphosate acid

d. *In vivo* micronucleus and chromosomal aberration assays

Numerous studies were evaluated to determine the potential for glyphosate to induce micronuclei in rodent bone marrow cells. Studies included both intraperitoneal (IP) and oral routes of glyphosate administration. In a literature study by Bolognesi *et a*l. (1997), the authors reported an induction of micronuclei in male mice treated with up to 300 mg/kg (IP injections as two ½ doses). It is noted that this study included only 3 animals/dose; rather than the 5 animals/dose recommended in the agency's test guideline (870.5395). Similarly, the route of administration is generally used for mechanistic studies but is not relevant to a human risk assessments. In another literature study, Manas *et a*l. (2009) reported an induction of micronuclei in BALB/C mice when tested up to 200 mg/kg glyphosate also by IP injection. Additionally, Suresh *et al.* (1993) reported an increase in micronuclei in females only in Swiss albino mice treated at the high dose of 5 mg/kg glyphosate; a dose that is more than twice the limit dose for the agency's guideline study. Additionally, this author was unable to duplicate this "positive' response in a repeat test using the same mouse strain and a comparable dose of the test material. Although the above authors reported positive findings, a vast majority of the *in vivo* genotoxicity studies (including the previously reviewed guideline mammalian micronucleus test) were negative at doses similar to or higher than the studies discussed above, regardless of the dosing regimen or route of administration. A summary of the findings are reported in Table 21.

Table 21. Results from *in vivo* genotoxicity assays[1].

Author	Assay Type	Species/strain	Purity	Dose	Results	Comments
Bolognesi *et al.* (1997)	Micronucleus test	Male mice (strain not provided)	99.9%	300 mg/kg Only dose tested	Positive	Two IP injections of ½ dose; 3 mice/dose
Durward, R. (2006)	Micronucleus test	Young adult male and female albino Crl:CD-1TM(ICR)BR mice	95.7%	600 mg/kg	Negative	Single IP injection; Significant increase in % PCEs per 1000 erythrocytes was observed in the 24-hour; however not 48-hour at 600 mg/kg
Flügge, C. (2009)	Micronucleus test	Male and female CD rats	98.8%	2000 mg/kg	Negative	Single dose; oral gavage
Fox and Mackay (1996)	Micronucleus test	Male and female CD-1 BR mice	95.6%[2]	5000 mg/kg	Negative	Single dose; oral gavage
Honavar, N.	Micronucleus	Male and female	97.73%	2000	Negative	Single dose; oral

(2005)	test	NMRI mice		mg/kg		gavage
Honavar, N. (2008)	Micronucleus test	NMRI male mice	99.1%	2000 mg/kg	Negative	Single dose; oral gavage
Jensen, J.C. (1991)	Micronucleus test	Young adult male and female NMRI SPF mice	98.6%	5000 mg/kg	Negative	Single dose; oral gavage
Manas et al. (2009)	Micronucleus	BALB/C mice	96%	50, 100, and 200 mg/kg	Positive at high dose	Two IP doses, 1 day apart
NTP (1992)	Micronucleus test	Male and female B6C3F1 mice	99%	11,379 mg/kg/day	Negative	Dietary admin., 13 weeks
Suresh, T.P. (1993)	Micronucleus test	Young Swiss albino male and female mice	98.6%	50, 500 and 5000 mg/kg	Males: Negative. Females: Positive at high dose only	Two doses 1 day apart; oral gavage
Suresh, T.P. (1994)	Mouse Bone Marrow Chromosome Aberration	Male and female Swiss albino mice	96.8%	5000 mg/kg	Negative	Two doses, 24 hours apart; oral gavage

1. Studies cited in Williams *et al.*, (2000), Kier and Kirkland (2013), or IARC monograph.
2. Glyphosate acid
3. IP= intraperitoneal injection

e. Other genotoxicity assays

Inconsistent responses were reported in number of assays designed to detect DNA damage, including sister chromatid exchange (SCE) assay, unscheduled DNA synthesis assay, and the comet assay (also known as the single cell electrophoresis assay). Positive responses in these assays do not necessarily indicate a chemical is either mutagenic or clastogenic, but rather that under the conditions of the assay, DNA damage did occurred. However, none of these assays take into account the likely possibility that the damage to DNA can and is often repaired. Glyphosate was negative in two rodent dominant lethal test and in two Rec- DNA repair tests in *B. subtilis*. The results of these genotoxicity studies are presented in Table 22.

Table 22. Additional genotoxicity assays

Authors	Assay Type	Cell Type	Purity	Highest test conc.	Results
Bolognesi et al. (1997)	Sister chromatid exchange (SCE)	Human Peripheral blood (in vitro)	99.9%	1000 ug/mL	Positive
Lioi et al. (1998a)	SCE	Human Peripheral blood (in vitro)	>98%	1.4 mg/L	Equivocal
Lioi et al. (1998b)	SCE	Bovine Peripheral blood (in vitro)	>98%	2.9 mg/L	Equivocal
Li and Long (1988)	Unscheduled DNA synthesis (UDS)	Rat hepatocytes (in vitro exposure)	98%	0.125 mg/mL	Negative

Table 22. Additional genotoxicity assays

Authors	Assay Type	Cell Type	Purity	Highest test conc.	Results
Rossberger, S. (1994)	UDS	Primary rat hepatocytes	98%	111.69 mM	Negative
Bolognesi et al. (1997)	DNA Damage/reactivity/ UDS	Mouse; IP administration	99.9%	300 mg/kg	Equivocal
Bolognesi et al. (1997)	DNA Damage/reactivity/ UDS	Mouse; IP administration; alkaline solution of extracted DNA	99.9%	300 mg/kg	Positive
Alvarez-Moya et al. (2014)	Comet assay	Human lymphocytes	96%[2]	700 µM	Positive
Lueken et al. (2004)	Comet assay	Human fibroblasts GM 5757	98.4%	75 mM	Negative
Manas et al. (2009)	Comet assay	Liver Hep-2 cells	96%	7.5 mM	Positive
Mladinic et al. (2009)	hGGO1 modified Comet assay[3]	Human lymphocytes	98%	580 ug/mL (toxic); approx 3.43 mM	Positive
Rossberger, S. (1994)	DNA repair test	Male SD rat primary hepatocytes	>98%	111.69 mM	Negative
Suresh, T.P. (1992)	Rodent dominant lethal test	Male and female Wistar rats	96.8%	500 mg/kg (single dose); 100 mg/kg (5 daily doses)	Negative
Wrenn (1980)	Rodent dominant lethal test	Mouse; gavage	98.7%	2000 mg/kg	Negative
Akanuma, M. (1995)	DNA repair test (Rec- assay)	*Bacillus subtilis* M45 rec-/ H17 rec+	95.68%[2]	240 ug/disk	Negative
Li and Long (1988)	DNA repair test (Rec assay)	*B. subtilis* H17, rec+; M45, rec-	98%	2 mg/disk	Negative

1. Studies cited in Williams *et al.*, (2000), Kier and Kirkland (2013), or IARC monograph.
2. Glyphosate acid
3. hOGG1= human 8-hydroxyguanine DNA-glycosylase (to detect oxidative damage)

f. Conclusions

In summary, glyphosate was not mutagenic in bacteria or mammal cells *in vitro*. Additionally, glyphosate did not induce chromosomal aberrations *in vitro*. Although some studies in the open literature reported positive findings for micronuclei induction in rodents, these findings were not replicated in the majority of the rodent micronuclei studies considered in this assessmnt by CARC. Some positive results were reported for the SCE and comet assays in the open literature; however, there is no convincing evidence that the DNA damage is a direct effect of glyphosate, but rather may be a secondary to cytotoxicity or oxidative damage as observed by Mladinic et al.(2009).

3. Structure-Activity Relationship

At present there are no structurally related pesticide registered by the Agency which resemble glyphosate. Sulfosate (the trimethylsulfonium salt of glyphosate, also known as glyphosate-trimesium) is a 1:1 molar salt of N-(phosphonomethyl) glycine anion (PMG) and the trimethylsulfonium cation (TMS). Sulfosate was evaluated for its carcinogenic potential following dietary administration to male and female mice at 0, 10, 1000 or 8000 ppm (equivalent to 0, 16, 159 or 1341 mg/kg/day, respectively) for 18 months, and in male and female Sprague-Dawley rats at 0, 100, 500 or 1000 ppm (equivalent to 0, 5.4, 27 or 557 mg/kg/day, respectively) for two years. There was no evidence of carcinogenicity in either species. Sulfosate is classified as a Group E Chemical; "not likely human carcinogen", based on the absence of carcinogenicity in mice and rats in two acceptable studies. Based on the available mutagenicity studies, there is no concern for mutagenicity (TXR No. 006452 and 011156).

4. Subchronic and Chronic Toxicity Studies

a. Subchronic Toxicity

In a 90-day feeding study in CD-1 mice (MRID No.: 00036803) were fed diets containing 0, 250, 500 or 2500 mg/kg/day of glyphosate for three months. Body weight gains of the high-dose males and females were about 24% and 18% lower, respectively, than those of the controls. Body weight gains of the low-dose and mid-dose groups were comparable to those of the controls. Based on the reduced body weight gains in both sexes, the NOEL for systemic toxicity is 500 mg/kg/day and the LOEL is 2500 mg/kg/day.

In a 90-day feeding study in Sprague-Dawley rats (MRID No.: 40559401), were fed diets containing 0, 1000, 5000 or 20000 ppm of glyphosate for three months. These doses were equivalent to 0, 63, 317 and 1267 mg/kg/day, respectively (males) and 0, 84, 404 and 1623 mg/kg/day, respectively (females). The following findings were regarded as possibly treatment-related: (1) increased sarum phosphorus and potassium in all treated groups, males and females; (2) increased serum glucose in the mid-dose and high-dose males; (3) increased blood urea nitrogen (BUN) and serum alkaline phosphatase in the high-dose males; and (4) occurrence of pancreatic lesions in the high-dose males (pancreas was not examined at the low-dose and mid-dose groups). Based on these findings, the systemic NOAEL is < 1000 ppm (not determined definitively) for both sexes

b. Chronic Toxicity

(i) Rats

A chronic feeding/carcinogenicity study (MRID No. 00093879) was conducted using male and female Sprague-Dawley rats which were fed diets containing 0, 30, 100 or 300 ppm of glyphosate for 26 months. These levels were equivalent to 0, 3, 10 and 34 mg of glyphosate/kg/day, respectively. There were no effects based on any of the parameters examined (toxic signs,

mortality, body weights, food consumption, hematology, clinical chemistry, urinalysis, organ weights and organ/tissue pathology). Therefore, the NOAEL for systemic toxicity is 300 ppm (males: 31 mg/kg/day and females: 34 mg/kg/day)

A second chronic feeding/carcinogenicity study (MRID No.: 41643801) was conducted using male and female Sprague-Dawley rats which were fed diets containing 0, 2000, 8000 or 20000 ppm of glyphosate for 2 years. These levels were equivalent to 0, 89, 362 or 940 mg/kg/day, respectively, for the males and 0, 113, 457 or 1183 mg/kg/day, respectively, for the females. Treatment-related effects observed only in the high-dose group included: (1) In the females: decreased body weight gains; and (2) In the males: increased incidence of cataracts and lens abnormalities, decreased urinary pH, increased absolute liver weight and increased liver weight/brain weight ratio {relative liver weight). No significant systemic effects were observed in the low-dose and mid-dose male and female groups. Therefore, the NOAEL for systemic toxicity is 8000 ppm (males: 362 mg/kg/day and females: 457 mg/kg/day) and the LOAEL is 20000.

In a combined chronic toxicity/carcinogenicity study (MRID No. 49631701), glyphosate (98.9% a.i) was administered to 85 Sprague-Dawley rats/sex/dose in the diet for 104 weeks in amounts that varied in concentration to deliver 0, 10, 100, 300, and 1000 mg/kg/day to both sexes over the course on the study. Designated for the toxicity portion of the study were 35 rats/sex/dose with the remainder designated for the oncogenicity portion of the study. An interim sacrifice was conducted on 15 rats/sex/dose after 52 weeks of glyphosate administration.

There were no statistical differences between treated and control groups in survival rates. Pale feces were observed during weeks 16-104 in both sexes at the high dose and in females from the low-mid and high-mid dose levels. No treatment-related effect was observed in food consumption, hematology, ophthalmology, and gross pathology data. Males from the high-dose group had statistically lower mean body weight ($p \leq 0.01$) by 5% to 11% beginning Week 2 of the study until Week 104, and at termination was 10% lower (-14% weight gain). Females at the high dose had statistically lower body weight ($p \leq 0.05$) by 5% to 12% beginning Week 20 through Week 80 (with several exceptions), and at termination was 8% lower (-11% weight gain). Statistically increased ALP activities (+46% to +72%) were observed in males at the high dose throughout the study except for the 51 week interval when the mean value was 31% higher than control. Elevated ALP activities were observed in females at the high dose (+34% to +53%) throughout the study, and through most of the study at the high-mid dose by +20% to +67%, though not always statistically significant. Urinalysis data showed reduced pH (5.5-6) in males at the high dose throughout the study.

The absolute liver weight was decreased significantly in females at the high dose after 52 weeks, but after correcting for final body weight the difference was statistically significant at the three highest doses. The parotid salivary gland weight was increased significantly in males at the three highest doses (56-111%) after 52 weeks, but not after 104 weeks. The combined weight of the sublingual and submaxillary salivary glands was significantly increased by 13% (22% after correcting for body weight) at the high dose after 52 weeks. In females, the parotid gland was not

affected but the sublingual and submaxillary combined weight was significantly higher by about 15%. The changes in salivary gland weights were accompanied by increased incidence of mild to severe parotid salivary gland cell alterations and slight to moderate mandibular salivary gland cell alterations were observed in both sexes at the 52-week and 104-week intervals. The lesions were described as cells and/or acini that appeared larger and stained in a weakly basophilic manner without showing a tendency toward proliferative or degenerative changes over time. In males, the increased incidence and severity of lesions in the parotid gland were significant ($p \leq 0.01$) at 100, 300, and 1000 mg/kg bw/day at 52 weeks, and significant at 300 and 1000 mg/kg bw/day at 104 weeks. The increased incidence of lesions in the mandibular gland were significant at 300 and 1000 mg/kg bw/day at 52 weeks and significant ($p \leq 0.001$) at 100, 300, and 1000 mg/kg bw/day at 104 weeks. In females, the increased incidence of parotid lesions was significant at 300 and 1000 mg/kg bw/day at 52 weeks, and significant at 100, 300, and 1000 mg/kg bw/day at 104 weeks. The increased incidence in the mandibular gland lesions was significant at the high dose at both 52 and 104 weeks. The incidence and/or severity of kidney nephropathy decreased in males at 100, 300, and 1000 mg/kg bw/day at 52 weeks and at the high dose at 104 weeks. Urothelial hyperplasia significantly decreased in females from the high dose group at both the 52-week and 104-week intervals. The LOAEL in male and female Sprague-Dawley rats administered glyphosate for 104 weeks in the diet was 100 mg/kg bw/day based on microscopic lesions in the parotid and mandibular salivary glands. The NOAEL was 10 mg/kg bw/day (MRID No. 49631701.

In another chronic toxicity/carcinogenicity study, groups of 52 male and 52 female Alpk:APSD (Wistar derived) rats were fed diets containing glyphosate at 0, 2000, 6000 or 20,000 ppm were fed for 2 years. These doses were equivalent to 0, 121, 361 or 1214 mg/kg/day in males and 0, 145, 437 or 1498 mg/kg/day in females. Treatment-related finding were confined to the liver and kidneys at the highest dose (20,000 ppm). In both sexes, treatment-related changes manifested as papillary necrosis, prostatitis, periodontal inflammation, urinary acidosis, and hematuria. The LOAEL was 20,000 ppm (1214 mg/kg/day in males and 1498 mg/kg/day in females) and the NOAEL was 6000 ppm (361 mg/kg/day in males and 437 mg/kg/day in females) (MRID 49704601).

(ii) Mice

In a carcinogenicity study (MRID 00251007), glyphosate (Technical, 99.7% a.i.) was administered to groups of 50 male and 50 female CD-1 mice/sex/dose in the diet at dose levels of 0, 1000, 5000, or 30,000 ppm (approximately equivalent to 0, 161, 835, 4945 mg/kg bw/day for males and 0, 195, 968, and 6069 mg/kg bw/day for females) for 24 months. Cage-side and detailed clinical observations were done. Body weight and food intake were monitored throughout the study. Water consumption was measured during months 12 and 24. Erythrocyte, as well as total white cell counts and differentials, were done at months 12, 18, and 24. Tissues and organs were collected from all mice whether dying during the study or at terminal sacrifice. Microscopic analyses were done on all collected tissues.

No treatment-related effects were found on survival, body weight, food or water consumption, or hematology parameters of treated male or female mice. The terminal body weight of high-dose males was significantly decreased 9% while the absolute liver weight of high-dose males was significantly decreased 16%; however, no significant treatment-related effects were found on the

liver to body weight ratio. The absolute testes weight of high-dose male mice was increased 7%, while the relative to body testes weight was increased 17. Neither were statistically significant, and no microscopic histological correlates were found. The incidences of centrilobular hepatocyte hypertrophy were slightly, but not significantly increased in high-dose male mice. Centrilobular hepatocyte necrosis was significantly increased in high-dose males (10/50** (20%) vs control 2/49 (4%), $p \leq 0.01$). No significant increases in centrilobular hepatocyte hypertrophy or necrosis were observed in treated female mice; however, proximal tubular epithelial basophilia was significantly increased in high-dose females (9/50 (18%) vs control 0/50 (0%), $p \leq 0.01$). No other microscopic treatment-related effects were found.

Based on increased centrilobular hepatocellular necrosis in high-dose males and proximal tubular epithelial basophilia in high-dose females, the systemic LOAEL for male and female CD-1 mice was 30,000 ppm (approximately 4945 mg/kg bw/day for males and 6069 mg/kg bw/day for females). The NOAEL for the study was 5000 ppm (approximately 835 mg/kg bw/day for males and 968 mg/kg bw/day for females) (MRID 00251007),

In another carcinogenicity study (MRID No.49631702), glyphosate (97.5 – 100.2% a.i.) was administered to groups of 50 CD-1 mice/sex/dose in the diet at doses of 0, 100, 300, or 1000 mg/kg bw/day for 104 weeks. No interim sacrifices were done. Mortality, body weight, body weight gain, and food consumption were monitored throughout the study. WBC differential counts were done during Weeks 52, 77, and 102 of the study. Following premature deaths or at scheduled sacrifice, organ weights were measured and tissues collected for microscopic analyses.

Treatment of male and female mice for 104 weeks did not increase mortality and did not decrease body weight, body weight gain or food consumption. No treatment-related clinical signs of toxicity were observed and no effects were found on WBC differential counts. Treatment did increase the absolute and relative thymus weights of male and female mice treated with 300 or 1000 mg/kg bw/day approximately 2 – 3 fold, but only the results of male mice were statistically increased. However, no treatment-related effects were found microscopically. At necropsy, the incidence of lung masses was slightly increased in high-dose male mice, but were considered coincidental. Microscopically, there was a slight, but statistically significant increase in mineral deposition in the brains of mid- and high-dose male mice. A non-significant increase was observed in female mice. Kidney cysts were also slightly but statistically increased in low- and mid-dose males, but no increase of cortical tubular eosinophilic droplets was found in female mice. The significance of these findings is questionable since they did not follow a dose-response. The systemic NOAEL for glyphosate in male and female CD-1 mice treated up to 104 weeks was 1000 mg/kg bw/day. A LOAEL was not identified (MRID No.49631702).

V. COMMITTEE'S ASSESSMENT OF THE WEIGHT-OF-THE-EVIDENCE

1. Evidence for Carcinogenicity in Humans

(i) Cancer at Multiple Sites

Several case-control studies reported no association for cancer of the oral cavity, colon, rectum, colorectum, lung, pancreas, kidney, bladder, prostate, breast or melanoma from exposure to glyphosate (De Roos *et al.*, 2005; Engle *et al.*, 2005; Lee *et al.*, 2007; Andreotti *et al.*, 2009; and Dennis *et al.*, 2010).

In single case-control studies, no associations were found for cancers of the esophagus, stomach, prostate or soft-tissue sarcoma from exposure to glyphosate (Alavanja *et al.*, 2003; Lee *et al*, 2004; Band *et al.*, 2011; Pahwa, *et al.*, 2011; Koutros *et al.,* 2013). No association for childhood cancer was found from maternal or paternal exposure to glyphosate (Flowers *et al.*, 2004).

(ii) Brain Cancer

A case-control study in Nebraska and the Upper Midwest Health case-control study in Iowa, Michigan, Minnesota and Wisconsin did not find any no association of glyphosate with adult brain cancer, specifically for gliomas (Ruder *et al.*, 2004; Carreon *et al.*, 2005; and Lee *et al.*, 2005).

(iii) Leukemia

No excess in leukemia was reported in a case-control study in Iowa and Minnesota (Brown *et al.*, 1990) or in the AHS cohort (De Roos *et al.*, 2005). A Swedish case-control study reported a non-statistically significant elevated risk for hairy cell leukemia. However, the authors stipulated that this risk should be interpreted with cautions since it was based on only 4 glyphosate-exposed cases (Nordstrom *et al.*, 1998)

(iv) Multiple Myeloma

No excess risk for multiple myeloma from exposure to glyphosate was found in three separate population-based case control studies: one in Iowa and Minnesota (Brown *et al.*, 1993) and the other in Iowa and North Carolina, USA (De Roos *et al.*, 2005; Sorhan 2015); and the third study in Canada (Pahwa *et al.*, 2012; Kachuri et al., 2013), and in a hospital-based case control study in France (Orsi *et al.*, 2009). A cohort study found no association with glyphosate exposure and monoclonal gammopathy of undetermined significance, a pre-clinical marker of multiple myeloma progression (Landgren *et al.*, 2009)

(v) Non-Hodgkin's Lymphoma

There is conflicting evidence for an association for NHL and glyphosate exposure; some reported no association while a two case-control studies from Sweden reported positive association.

.No association with glyphosate exposure and NHL was found in three population-based case control studies in the United States: in Iowa and Minnesota (Cantor *et al.*, 1992); in Iowa, Nebraska and Minnesota (Lee *et al.*, 2004a); in Iowa, Nebraska, Minnesota and Kansas (De Roos *et al.*, 2003) and in the AHS cohort with 57,311 licensed pesticide applicators in Iowa and North Carolina (De Roos *et al.*, 2005).

Similarly, no association was seen in population-based case control studies conducted in various Canadian provinces (McDuffie et al., 2001; Hohenadel et al., 2011).

A hospital based case-control study from France did not find an association between glyphosate exposure and NHL (Orsi *et al.*, 2009).

The first report of an association of glyphosate with NHL was in a population-based case control study in Sweden (OR=23.3; 95% CI=0.40-13.0); however, this was based on only 4 glyphosate-exposed cases and 3 controls (Hardell and Erickson, 1999).

In a 2002 follow-up study, data from two case-control studies in Sweden, one on NHL and the other on hairy cell leukemia, were pooled and analyzed. A univariate analysis showed an increased risk (OR=3.04; 1.08-8.52); however, when study site, vital status, and exposure to other pesticides were taken into account in a multivariate analysis, risk declined (OR=1.85; 95% CI=0.55-6.20) (Hardell *et al.*, 2002).

In another case-control study in Sweden, among the 29 glyphosate-exposed cases, there was a statistically significantly increased risk for NHL (OR=1.51; 95% CI=0.77-2.94) and B-cell lymphoma (OR=1.87; 95% CI=0.998-3.51) in the multivariate analysis.

In summary, there was no consistent patterns of statistically significant positive association between glyphosate exposure and NHL. A statistically significant positive association for NHL and glyphosate exposure was reported in one Swedish case-control study. The finding in this study, however, should be evaluated further for study bias, confounders and sampling errors before establishing causality. However, a meta-analysis utilizing six of the above studies examining glyphosate and NHL found a significant increased meta-risk ratio. In contrast, there was no association with any site-specific cancer or NHL and lifetime exposure to glyphosate in the large prospective cohort study of 57,311 licensed pesticide applicators in AHS.

In assessing the weight-of-evidence of epidemiologic studies which relate to glyphosate exposure,

one has to make a subjective judgment as to the weights given for the various studies and their conflicting conclusions. As discussed above, there are diverse results from many of the studies; some have shown a relationship between glyphosate and NHL and some did not observe an association. However, there are inconsistencies in the results (even of the positive Swedish study) which raise doubts as to whether the relationship is causal with the current status of the literature. Thus while epidemiologic literature to date does not support causal association, continued following of the glyphosate and NHL literature is warranted. Furthermore, there is no support from animal data to make the case for causation, particularly by establishing biologic plausibility and the existence of potential mechanism since there was no evidence for carcinogenicity twelve studies conducted in mice or rats.

2. Evidence for Carcinogenicity in Experimental Animals

a. Evidence for Carcinogenicity in Rats

A total of seven chronic toxicity/carcinogenicity studies in Wistar or Sprague-Dawley strain rats were available for review. In these studies, glyphosate was administered in the diet to both sexes at doses ranging from 3.0 mg/kg/day to 1500 mg/kg/day for 2-years. In 4 of 7 studies there were no biologically or statistically significant increases in the occurrence of any tumor types. Tumors observed in the other three studies are discussed below.

(i) Testes

In Sprague-Dawley rats (MRID No. 00093879), there was a non-dose related increase in the incidences of interstitial cell tumors in the testes of males at 3 mg/kg/day (6%), 10 mg/kg/day (2%) and 30 mg/kg/day (12%; P=0.013) when compared to controls (0%). The CARC reaffirmed the previous conclusion that these tumors are treatment related based on the following considerations: 1) lack of dose-response; 2) absence of preneoplastic lesions (*i.e*, interstitial cell hyperplasia); 3) the incidences were within the normal biological variation seen for this tumor type in this strain of rats; 4) the incidences in the concurrent controls (0%) was not representative of the normal background incidences noted in the historical control animals (mean, 4.5; range, 3.4% to 6.7%;) and 5) this finding is not replicated in the other studies in the same strain of rats (i.e, no interstitial cell tumors were seen when tested up to1100 mg/kg/day).

(ii) Pancreas

Benign pancreatic islet cell tumors were seen in male Sprague-Dawley rats in two studies. In the first study (MRID No. 00093879), there was no dose response or statistical significance; the incidences for adenomas were: 0%, 10%, 4% and 4% at the control, low, mid and high dose groups. Carcinomas were seen in one rat at the high dose. In the second study (MRID No. 4172800), there was a statistically significant increase in adenomas at the lowest (100 mg/kg/day) and the highest (1000 mg/kg/day) doses compared to controls: lowest dose, 8/45 (18%; p=0.018); intermediate dose, 5/49 (10%); and highest dose, 7/48 (15%; P=0.042) versus controls, 1/43 (2%).

The CARC reaffirmed the previous conclusion that the benign pancreatic islet cell tumors are not treatment due to lack of dose-response, absence of preneoplastic lesions, there was no progression to malignancy, and the incidences were within the historical control range (0-17%) reported for this tumor in this strain of rats. This neoplasm was not seen in the other six studies.

(iii) Liver

In male Sprague-Dawley rats (MRID No.41728700), there was a statistically significant positive trend in the incidence of hepatocellular adenomas (P=0.016). The CARC concluded that the minimal increase in adenomas is not treatment-related due lack of statistical significance in pairwise comparison, absence of preneoplastic lesions, no progression to malignancy, and the incidences were within the historical control range (1.4 – 18.3%) of the testing laboratory.

In male Wistar rats (MRID No.49704601), there was a there was a statistically significant trend (p=0.00804) and pairwise significance for the increase in hepatocellular adenomas at the highest (1214 mg/kg/day) dose compared to controls: lowest dose, 2/52 (4%); intermediate dose, 0/52 (0%); and highest dose, 5/52 (10%; P=0.02826) versus controls, 0/52 (0%). The CARC conclude that this increase is not attributable to treatment based on the following considerations: 1) absence of dose-response relationship; 2) lack of progression to malignancy; 3) no evidence of pre-neoplastic lesions; 4) the incidences were within the historical control range (0-11.5%).

The CARC noted that survival was better at the high dose (25/52; 13%) compared to the controls (16/52; 8.3%) which could be reason for the slightly higher incidence (5/52) of this age-related background tumor like liver adenomas in the absence of any associated lesions. Furthermore, with a weak genotoxic effect one would expect to see an effect on carcinomas (or at least adenomas/ carcinomas, combined) and shorter latency period, which were not observed in this study. With a weak cytotoxic or mitogenic effect one would expect to see an increase in foci and other non-neoplastic lesions. In addition, as discussed above, only a linear trend (no pairwise) was seen for this tumor type in another strain (Sprague-Dawley) for rats where the incidences were still within the historical control range. Also, liver tumors were not seen in the other four studies. This provides additional evidence for lack of an actual carcinogenic response in the liver.

(iv) Thyroid

In female Sprague-Dawley rats (MRID No.41728700), there was a statistically significant positive trend in the incidence of thyroid C-cell tumors in males (P=0.031). The CARC concluded that the minimal increase is not treatment-related due to lack of statistical significance in pairwise comparison, no progression to carcinomas, no increase in severity of grade or incidence of hyperplasia, and the incidences were within the historical control range (3.3 – 10%).

In summary, the observed tumors did not show statistical significance, dose-response relationship, no progression to malignancy, and/or the incidences were within the background and/or historical control range for the type of tumors in that particular strain

and age of rats. Dietary administration of glyphosate at doses ranging from 3.0 to 1500 mg/kg/day for up to 2 years produced no evidence of carcinogenic response to treatment in male or female Sprague-Dawley or Wistar rats.

b. Evidence for Carcinogenicity in Mice

Four carcinogenicity studies in CD-1 mice were available for review. In these studies, glyphosate was administered in the diet to both sexes at doses ranging from 85 mg/kg/day to 4800 mg/kg/day for 18-24 months. In one study there were no biologically or statistically significant increases in the occurrence of any tumor types. Tumors observed in the other three studies are discussed below.

(i) Kidney

Kidney (renal tubular) tumors were seen in male CD-1 mice (MRID No. 00251007). The incidences of adenomas was 1/49 (2%), 0/49 (0%), 0/50 (0%), and 1/50 (2%) in the control (0 mg/k/day), low (157 mg/kg/day), mid (814 mg/kg/day) and high (4945 mg/kg/day) dose groups, respectively. The incidence of carcinomas was 0/49 (0%), 0/49 (0%), 1/50 (2%) and 2/50 (4%) in the control, low, mid and high dose groups, respectively. The incidence of adenomas or carcinoma (combined) was 1/49 (2%), 0/50 (0%), 1/50 (2%), 3/50 (6%) in the control, low, mid and high dose groups, respectively. None of these differences showed statistical significance.

The CARC reaffirmed the previous conclusion that the kidney tumors are not treatment-related based on the following weight-of-evidence considerations: a) lack of dose-related trend or statistical significance in pairwise comparisons; b) lack of non-neoplastic renal tubular lesions (e.g. tubular necrosis/regeneration, hyperplasia, hypertrophy etc); c) the examination of multiple sections of kidneys from all groups resulted in no additional neoplasms; this fact is particularly important since not only were the original sections closely scrutinized by more than one pathologist, but additional sections as well; and d) the incidence in high dose group was very small compared to control considering the very high concentration (4 x time the limit dose).

Furthermore, the Pathology Work Group concluded that the renal tumors were not treatment-related since none of the treatment groups differed from the controls for a linear trend or pairwise statistical significance, there was no treatment-related nephrotoxic lesions including preneoplastic changes, and multiple renal tumors were not seen in any animal.

In addition, the CARC noted that this neoplasm was not observed when tested at a similar dose (4348 mg/kg/day) in this strain of mice in another study (Arysta, 1997b) or in two other studies at doses ranging from 100 to 1000 mg/kg/day (MRID No. 49631702, Nufarm, 2009b).

(ii) Lung

There was a dose-dependent increase in the incidence of bronchiolar-alveolar adenocarcinoma of the lung in male CD-1 mice (Nufarm, 2009b). There was a positive trend (P=0.00296) in the

incidence of lung adenocarcinomas: 5/51 (10%), 5/51 (10%), 7/51 (14%) and 11/51 (22%) at the 0, 85, 267 or 946 mg/kg/day groups, respectively. The CARC determined that this increase is not treatment-related due to lack of statistical significance in pairwise comparison, absence of pre-neoplastic lesions in the lung (e.g., bronchiolar-alveolar hyperplasia), and the incidences in all treated groups were within the background range (1.42 – 26%) for this tumor in this strain and age of mice. Also, lung tumors were not seen when tested at a comparable dose (1000 mg/kg/day) or at considerably higher (4116 - 4945 mg/kg/day) doses in this strain of mice in the other three studies (MRID No. 00251007; 49631702; Arysta, 1997b).

(iii) Malignant Lymphomas

There was a dose-dependent and statistically significant increase in the incidence of malignant lymphomas in male mice (Nufarm, 2009b). The incidence was: 0/51 (0%; P=0.006633), 1/51 (2%), 2/51 (4%) and 5/51 (10%; P=0.2820) at the 0, 85, 267 or 946 mg/kg/day groups, respectively. The CARC determined that this increase is not treatment-related since the incidences in the concurrent controls (0%) was not representative of the normal background incidences noted in the historical controls (mean, 4.5; range, 1.5% to 21.7%;), and the apparent statistical significance of the pairwise comparison of the high dose group with the concurrent control might have been attributable to this factor and to actual carcinogenic response. Also, this neoplasm was not seen in this strain of mice (MRID No. 00251007; 49631702; Arysta, 1997b).

(iv) Multiple Organs

Hemangiosarcomas were seen in multiple organs including, the liver, spleen, and prostate in males and the liver and uterus in female CD-1 mice (MRID No. 49631702). There was a positive trend (P=0.00296) in the incidence of hemangiosarcomas in male mice: 0/47 (0%), 0/46 (0%), 0/50 (0%) and 4/45 (9%) at the 0, 100, 300 and 1000 mg/kg/day groups, respectively. The hemangiosarcomas were present in the liver, spleen or prostate in the high dose males. In females, this neoplasm was seen in one female at the low dose (uterus) and in one high dose (spleen). The CARC did not consider the hemangiosarcomas in males to be treatment-related based on the following considerations: 1) there was no pairwise significance; 2) lack of dose-response;3) the incidence was near or the same as the upper limit (0-8%) of the background rate at the performing laboratory; 4) hemangiosarcomas are commonly observed in mice as both spontaneous and treatment-related tumors arising from endothelial cells; 5) is seen in both sexes but are generally more common in males in CD-1 strain mice; and 6) hemangiosarcomas were not seen when tested at comparable (946-1467 mg/kg/day) or at considerably higher doses (4116-4945 mg/kg/day) in this strain of mice in the other studies (MRID No.00251007, Arysta, 1997b, Nufarm, 2009b).

The CARC also noted that as vascular tumors, hemangiosarcomas can occur at different sites but liver and spleen tend to be the most common sites in male mice. Several studies have also looked at potential mode of action (MOA) for these tumors in response to various drugs or chemicals. These MOAs generally relate to hypoxia as an early key event. One study also noted an association between chemical-induced liver hemangiosarcomas and Kupffer cell pigmentation in

mice (Nyska et al. 2004). Hemangiosarcomas have a similar histopathologic appearance in rodents and humans but differ in both incidence and tissue site. In human populations, hemangiosarcomas have an incidence rate of approximately 0.2 new cases/100,000 people (0.0002%) (1996-2000, US National Cancer Institute–SEER Database) and account for < 1% of all human sarcomas. The historical background incidence of hemangiosarcomas in B6C3F1 and CD-1 mice relative to the incidence rate in humans has thus been estimated to be approximately 10,000-fold higher than in people (Pegg *et al* 2012). The most common sites for spontaneous hemangiosarcomas in rodents are liver, spleen, bone marrow and to a lesser extent in lymph nodes and skin (see references in Pegg *et al* (2012). Human hemangiosarcoma is most commonly reported in skin, particularly on the head and neck of elderly individuals ([HYPERLINK "http://toxsci.oxfordjournals.org/content/128/1/9.full" \l "ref-55"]). Primary liver hemangiosarcoma in humans has been linked to chemical exposure, notably thorotrast and vinyl chloride, which are both considered genotoxic carcinogens. There are several examples of induction of hemangiosarcomas by non-genotoxic agents in mice (see Cohen *et al* 2009) but no clear examples of hemangiosarcoma induction by non-genotoxic agents in human populations.

In summary, the observed tumors did not show statistical significance, dose-response relationship, no progression to malignancy, and/or the incidences were within the background and/or historical control range for the type of tumors in that particular strain and age of mice. Dietary administration of glyphosate at doses ranging from 85 to 4945 mg/kg/day for up to 2 years produced no evidence of carcinogenic response to treatment in male or female CD-1 mice.

c. **Discussion**

The Internation Agency for Research on Cancer (IARC) identifies a cancer "hazard" if an agent (*i.e.*, chemical) is capable of causing cancer under some circumstances and the agent is termed 'carcinogenic' if it is capable of increasing the incidence of malignant neoplasms, reducing their latency, or increasing their severity or multiplicity. The IARC also considers that there is "*sufficient evidence of carcinogenicity"* based on the occurrence of increased tumors (benign, malignant, or combination) in: 1) two or more species of animals; 2) two or more independent studies in on species; and 3) an increased incidence of tumors in both sexes of a single species. Furthermore, a single study in one species and sex might be considered to provide *sufficient evidence of carcinogenicity* when malignant neoplasms occur to an unusual degree with regard to incidence, site, type of tumor or age at onset, or when there are strong findings of tumors at multiple sites (IARC Preamble, 2006).

In 2015, the IARC evaluated the carcinogenic potential of a number of organophosphates and herbicides, including, glyphosate. The IARC determined that there was a positive trend in the incidence of renal tubular carcinoma and of renal tubule adenoma or carcinoma (combined) in males in one feeding study in CD-1 mice. Renal tubule carinoma is a rare tumor in this strain of mice. In the second feeding study, there was a significant positive trend in the incidence of hemangiosarcomas in male CD-1 mice. Thus, in accordance with one of the preamble criteria, "the

occurrence of tumors in two studies in one species", IARC classified that there is "sufficient evidence" in experimental animals for the carcinogenicity of glyphosate (IARC, 2015)

In contrast, the USEPA's carcinogenicity classification is based on a weight-of-evidence considerations in accordance with the agency's 2005 Guideline for Carcinogen Risk Assessment. The cancer guidelines emphasize the importance of weighing all of the evidence in reaching conclusions about the human carcinogenic potential of agents. This is accomplished in a single integrative step after assessing all of the individual lines of evidence. Evidence considered includes tumor findings, or lack thereof, in humans and laboratory animals; an agent's chemical and physical properties; its structure-activity relationships (SARs) as compared with other carcinogenic agents; and studies addressing potential carcinogenic processes and mode(s) of action, either *in vivo* or *in vitro*. Data from epidemiologic studies are generally preferred for characterizing human cancer hazard and risk. However, all of the information discussed above could provide valuable insights into the possible mode(s) of action and likelihood of human cancer hazard and risk (USEPA, 2015).

Conclusions for evidence of carcinogenicity are based on the combined strength and coherence of inferences appropriately drawn from all of the available information. The following observations add significance to the tumor findings: tumors in multiple species, strains or both sexes; dose-related increases; progression of lesions from preneoplastic to benign to malignant; proportion of malignant tumors; reduced latency of neoplastic lesions; and both biological and statistical significance of the findings. (USEPA, 2005).

The IARC attributed the kidney tumors observed in male CD-1 mice at the high dose in the feeding study (MRID No. 00251007) to treatment since they are rare and there was a dose-related trend for carcinoma (P=0.034) and combined adenoma or carcinoma (P=0.037) in a Cochran-Armitage trend test. However, as shown in Table 14, agency's statistical analyses (Fisher exact trend test) did not show significant trend for either carcinoma (P=0.06345) or the combined adenoma or carcinoma (P=0.06483). In a Fisher's exact test, there was no pairwise significance for any tumor type (adenoma, carcinoma, or combined). There were no pre-neoplastic renal tubular lesions such as tubular necrosis/regeneration, hyperplasia or hypertrophy. Examination of multiple sections of kidneys from all animals by more than one pathologists did not result in any additional neoplasms. Although the highest dose tested (4945 mg/kg/day) was approximately 5-fold higher than the limit dose (1000 mg/kg/day) recommended by the agency's guideline, the incidence of the kidney tumors was minimal (1/50 adenomas and 2/50 carcinomas) compared to controls (1/49, adenomas). An evaluation by the independent Pathology Work Group (PWG) concluded that the renal tumors are not treatment-related since there were no compound related nephrotoxic lesions, including preneoplastic changes, multiple tumors were not found in any animals and there was no evidence of a significant linear trend at the 0.5 level in a one-tailed Cochran-Armitage test or pairwise significance in a Fisher's exact test. Furthermore, kidney tumors were not seen when tested at lower (85 to 1000 mg/kg/day) or at a comparable (4116 mg/kg/day) in this strain of mice

in the other three studies. Thus, the totality of data available from four carcinogenicity studies provides a strong support for the conclusion that the kidney tumor seen in one study is not the result of a carcinogenic response by glyphosate.

The IARC attributed the hemangiosarcomas observed in male CD-1 mice at the high dose in another feeding study (MRID No. 49631702) to treatment due to the positive trend ($P < 0.001$) in a Cochran-Armitage trend test. As shown in Table 15, agency's statistical analyses also showed a positive trend ($P=0.00296$) in the Fisher's exact trend test. There was no pairwise significance when compared to controls. In contrast with the IARC, the CARC did not consider the hemangiosarcomas to be treatment-related based on the following weight of evidence considerations: 1) there was no pairwise significance; 2) lack of dose-response; 3) the incidence was near or the same as the upper limit (0-8%) of the background rate at the performing laboratory; 4) hemangiosarcomas are commonly observed in mice as both spontaneous and treatment-related tumors arising from endothelial cells; 5) this tumor is seen in both sexes but are generally more common in males in CD-1 strain mice; and 6) hemangiosarcomas were not seen when tested at comparable (946-1467 mg/kg/day) or at considerably higher doses (4116-4945 mg/kg/day) in this strain of mice in the other studies (MRID No.00251007, Arysta, 1997b, Nufarm, 2009b). It is noted that JMPR in their evaluation also concluded that the hemangiosarcomas are not treatment-related owing to lack of dose-response relationship, lack of statistical significance and the incidences were within the historical control range (JMPR, 2004).

The CARC also noted that as vascular tumors, hemangiosarcomas can occur at different sites but liver and spleen tend to be the most common sites in male mice. Several studies have also looked at potential mode of action (MOA) for these tumors in response to various drugs or chemicals. These MOAs generally relate to hypoxia as an early key event. One study also noted an association between chemical-induced liver hemangiosarcomas and Kupffer cell pigmentation in mice (Nyska et al. 2004). Hemangiosarcomas have a similar histopathologic appearance in rodents and humans but differ in both incidence and tissue site. In human populations, hemangiosarcomas have an incidence rate of approximately 0.2 new cases/100,000 people (0.0002%) (1996-2000, US National Cancer Institute–SEER Database) and account for < 1% of all human sarcomas. The historical background incidence of hemangiosarcomas in B6C3F1 and CD-1 mice relative to the incidence rate in humans has thus been estimated to be approximately 10,000-fold higher than in people (Pegg *et al* 2012). The most common sites for spontaneous hemangiosarcomas in rodents are liver, spleen, bone marrow and to a lesser extent in lymph nodes and skin (see references in Pegg *et al* (2012).Human hemangiosarcoma is most commonly reported in skin, particularly on the head and neck of elderly individuals ([HYPERLINK "http://toxsci.oxfordjournals.org/content/128/1/9.full" \l "ref-55"]). Primary liver hemangiosarcoma in humans has been linked to chemical exposure, notably thorotrast and vinyl chloride, which are both considered genotoxic carcinogens. There are several examples of induction of hemangiosarcomas by non-genotoxic agents in mice (see Cohen *et al* 2009) but no clear examples of hemangiosarcoma induction by non-genotoxic agents in human populations.

In summary, the IARC and the agency concurred that there is no evidence of carcinogenicity in

male or female rats or female mice. However, they differ in their conclusions on the evidence for carcinogenicity only in male mice.

3. Mutagenicity

Glyphosate was not mutagenic in bacteria or mammal cells *in vitro*. Additionally, glyphosate did not induce chromosomal aberrations *in vitro*. Although some studies in the open literature reported positive findings for micronuclei induction in rodents, these findings were not replicated in the majority of the rodent micronuclei studies considered in this assessmnt by CARC. Some positive results were reported for the SCE and comet assays in the open literature; however, there is no convincing evidence that the DNA damage is a direct effect of glyphosate, but rather may be a secondary to cytotoxicity or oxidative damage as observed by Mladinic et al.(2009).

4. Structure Activity Relationship

Sulfosate is classified as a Group E Chemical; "not likely human carcinogen", based on the absence of carcinogenicity in mice and rats in two acceptable studies. Based on the available mutagenicity studies, there is no concern for mutagenicity (TXR No, 011156).

VI. CLASSIFICATION OF CARCINOGENIC POTENTIAL

VII. QUANTIFICATION OF CARCINOGENIC POTENTIAL

VIII. BIBLIOGRAPHY

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